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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,145	03/23/2007	Istvan Eros	23565	9304

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EXAMINER	
KADAMBI, GEETA	
ART UNIT	PAPER NUMBER
4131	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,145	EROS ET AL.	
	Examiner	Art Unit	
	GEETA KADAMBI	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *29,31,33,35,37,39,41,43,45,47,49,51,53 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,8,9,12-14,17,18,20,22,24,26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,2,5,8,9,12-14,17,18,20,22,24,26,28,29,31,33,35,37,39,41,43,45,47,49,51,53 and 55.

DETAILED ACTION

1. Claims 1, 2, 5, 8, 9, 12, 13, 14, 17, 18, 20, 22, 24, 26, 28, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53 and 55 are pending.

2. Claims 1, 2, 5, 8, 9, 12, 13, 14, 17, 18, 20, 22, 24, 26 and 28 are under examination.

Election/Restrictions

3. Applicant's election with traverse of restriction election in the reply filed on 2/20/2008 is acknowledged. The traversal is on the ground(s) that special technical feature is hyaluronic acid and not polyoxyethylene glyceryl trioleate. However it is noted that for the transdermal patch all four components, namely polyoxyethylene glyceryl trioleate, propylene glycol, isopropyl myristate and hyaluronic acid are necessary for all the claims and the variables species are the active agents. Upon further consideration the restriction election is withdrawn and the composition and method claims are rejoined.

4. This application contains claims directed to the following patentably distinct species:

Claims 17 and 28 are generic to the following disclosed patentably distinct species:

1. Estrogen and progestin
1. Ondansetron
2. Terbinafine
3. Fluconazole
4. Metronidazole
5. Fenanyl
6. Nandrolone decanoate
7. Nestrone
8. Norethisterone
9. Eperisone

10. Tolperisone
11. Vinpocetine
12. Ketamine
13. Vincristine
14. Vinblastine

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1 and 17 are generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.
Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

5. During a telephone conversation with Attorney Jonathan Myers on April 10, 2008 a provisional election was made without traverse to prosecute the invention of elected species estrogen and progestin, claims 18, 20, 22 and 24. Affirmation of this election must be made by applicant in replying to this Office action. **Claims 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53 and 55 are**

withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species.

Claim Objections

6. Claims 5, 8, 9, 12, 20, 22 and 24 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to the claims in alternate only. See MPEP § 608.01(n). In the instant case it would be proper to change the statements "any of claims 1-4" to "any one of claims 1-4". This example is only for claim 5.

7. Claims 5, 8, 9, 12-14, 20, 22 and 24 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim depend on canceled claims. See MPEP § 608.01(n).

8. Claims 5, 8, 9, 12-14, 20, 22 and 24 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim can not depend on another multiple depended claim.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 5, 8, 9,12-14, 20, 22, 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant application the multiple dependent claims depend on cancelled claims. The applicant is requested to further clarify.

11. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the limitations of cancelled claims 3 and 4.

In order to expedite prosecution, claim 5 will be examined as being dependant from claims 1 and 2, as has apparently been intended.

12. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the limitations of cancelled claims 3, 4, 6 and 7.

In order to expedite prosecution, claim 8 will be examined as being dependant from claims 1, 2 and 5 as has apparently been intended.

13. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the limitations of cancelled claims 3, 4, 6 and 7.

In order to expedite prosecution, claim 9 will be examined as being dependant from claims 1, 2, 5 and 8 as has apparently been intended.

14. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the limitations of cancelled claims 3, 4, 6, 7, 10 and 11 are canceled.

In order to expedite prosecution, claim 12 will be examined as being dependant from claims 1, 2, 5, 8 and 9 as has apparently been intended.

15. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the limitations of cancelled claims 3, 4, 6, 7, 10 and 11 are canceled.

In order to expedite prosecution, claim 13 will be examined as being dependant from claims 1, 2, 5, 8 and 9 as has apparently been intended.

16. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the limitation of cancelled claim 19 is canceled.

In order to expedite prosecution, claim 20 will be examined as being dependant from claims 17 and 18 as has apparently been intended.

17. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the limitations of cancelled claim 19 are canceled.

In order to expedite prosecution, claim 5 will be examined as being dependant from claims 17 and 18 as has apparently been intended.

18. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the limitation of cancelled claim 19 is canceled.

In order to expedite prosecution, claim 24 will be examined as being dependant from claims 17 and 18 as has apparently been intended.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

21. Claims 1, 2, 5, 8, 9, 12, 13, 14, 17, 18, 20, 22, 24, 26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szab et al. (EP 509761) and Bunschoten et al. (US patent publication 2004/0192620) in view of

Parab PV (US 5326566), Brynhildsen et al. (Menopause 2002) (abstract only) in further view of Pouyani et al. (US 5616568).

Applicant is claiming a liquid crystal gel for use in the manufacture of transdermal pharmaceutical composition containing polyoxyethyleneglyceryl trioleate, propylene glycol, isopropyl myristate and hyaluronic acid salt or complex. They further claim polyoxyethyleneglyceryl trioleate in the weight range of 26.7 -40% to the total weight of the composition. Applicant also claims propylene-glycol between 13.3 and 20%, isopropyl myristate is between 5 – 35%, and ratio of polyoxyethyleneglyceryl trioleate to polypropylene glycol is 2:1. They specifically claim sodium and zinc salts of hyaluronic acid and the range is 0.01-2% of the total weight of the gel. Applicant further claims the composition consists of estrogen, specifically estradiol, gestodene, etonogestrel or levonorgestrel.

Szab et al. teaches the use of lyotropic liquid (liquid crystal gel) for a dermal preparation which assures a sufficient and uniform release of the active ingredient (pg 2, lines 29-30) (claims 1, 17and 28). Szab et al. also teaches the making of lyotropic liquid crystalline system by varying the quantity of the components to the particle size of the liquid crystal and the ratio of the liquid crystalline arrangement compared to the total system for ensuring uniform release corresponding to the therapeutic demands (pg 2, lines 37-41). Szab et al. further teaches the addition of 40-70 wt. % of liquid polyoxyethylene and 10-20 wt. % of solid polyoxiethylene and 2- 20% wt. % of propylene glycol (pg 2, lines 45-50) (claims 2 and 3). Szab et al. teaches the use of various polyoxiethylene

compounds (pg 2, 53- 57) and refers to them as PEG's in their example tables V (pg 6 and pg 7). Szab et al. teaches the procedure to make the composition and describes the method of adding polyoxiethylene (liquid and solid) with polyethylene glycol (pg 3, lines 7-10) and then adding the active ingredient (pg 3, lines 11-12). Szab et al. teaches the combination of polyoxyethylene and propylene glycol in the range that the applicant claims and also mentions addition of active agents to the mix. Szab et al. uses the hyaluronic acid as a polymer to make the liquid crystalline gel, hence creating the ideal environment for controlled and uniform release of the drug in a transdermal patch.

Szab et al. does not teach the use of sodium and zinc hyaluronate salts, isopropyl myristate and specifically use of hormones as active agents.

Bunschoten et al. teaches the use of a method of contraception by administration of estrogenic component and a progestogenic component (0069) as a transdermal patch among other formats (0042) (claims 17, 18, and 26). Bunschoten et al. also teaches the use of levonogestrel, etonogestrel and gestodene (0082) (claims 20, 22, 24). Bunschoten et al. further teaches that transmucosal delivery systems include patches among others and contain excipients such as solubilizers, e.g. propylene glycol and other vehicles e.g., fatty acid esters and hydrophilic polymers such as hyaluronic acid (0092) (claims 1 and 28). Suitable penetration enhancing agents such as isopropyl myristate and propylene glycol are among others (0120) (claims 1, 17 and 28). Isopropyl myristate is used by Bunschoten et al. as a suitable penetration enhancer for the estrediol and progestin compounds in transdermal patch.

Bunschoten et al. does not teach the use of polyoxyethylene glycol trioleate and the weight ratio of isopropyl myristate.

Parab PV teaches that the mixture of isopropyl myristate (IPM) and dibutyl adipate (DBA) enhances and controls the epidermal, dermal and transdermal penetration of various topically applied pharmacological agents (column 3, lines 60-65). IPM is known as a penetration enhancer for topical application and use of a combination with DBA provides synergistic effect and devoid of side effects. Parab PV also teaches that it is novel agents that enhance and/or control epidermal and dermal absorption of dermatological agents and enhance and control delivery of systemically active therapeutic agents through skin and into the general circulation. Parab PV also mention that the pharmacological agents such as steroids specially gesterone, estradiol, progesterone along with other examples. The concentration of IPM is between the ranges of 1-30% by weight of the composition (column 7, lines 8-10) (claim 9). Parab PV also teaches the addition of propylene glycol as a penetration enhancer in example 2 and the weight is 7% of the whole composition. The weight ratio between DBA and propylene glycol is 2:1 (claim 8). Parab PV further teaches that it is suitable for a patch along with others. The teachings of Parab PV suggest that the ratio adjustment between various chemicals that enhance the penetration of the drug via a transdermal patch helps create an ideal combination.

Parab PV does not teach the use of hyaluronic acid as permeation enhancer.

Pouyani et al. teaches that hyaluronic acid (HA) degrades very soon and functionalized or crosslinked HA facilitates subsequent attachment of additional components such as bioaffecting agents including drugs (column 2, lines 50-54). Pouyani et al. further teaches that hyaluronate posses a number of characteristics that make it advantageous to be used as a drug carrier as it is biocompatible, non-immunogenic and degrades in the body by enzymes , and possesses many covalent groups that are amenable for modification (column 3, lines 60-65). HA often occurs naturally as sodium salts (column 4, lines 8-10) (claim 12, 13 and 14). One ordinary skill in the art would substitute sodium with any other elements that are known to provide stability to hyaluronic acid. Transdermal patches would benefit from the use of stable hyaluronic acid in salt forms that enables HA to be a better drug carrier.

Brynhildsen et al. teaches the use of transdermal patch containing estradiol/norethisterone acetate to treat postmenopausal women (claim 26).

It would be prima facie obvious to combine polyoxyethylene glyceryl trioleate, isopropyl myristate, propylene glycol and hyaluronic acid in liquid crystal gel as compositions each of which is taught by the prior art to be useful for the same purpose to form a composition for a transdermal patch to be used for the very same purpose with a known bioactive component. The idea of combining them flows logically from their having been individually taught in the prior art.

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the

general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." (MPEP 2144.05)

One would be motivated to make this combination of the biocompatible, permeation enhancers to deliver the bioactive drugs transdermally with low immunogenic response. Given the state of the art as evidenced by the teachings of the cited references there would have been a reasonable expectation of success in combining the teachings of the cited references to obtain a composition of hormones that has effective pharmaceutical and therapeutic effect in the form of a transdermal patch.

CONCLUSIONS

All claims are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GEETA KADAMBI whose telephone number is (571) 270-5234. The examiner can normally be reached on Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public

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/Janet L. Andres/
Supervisory Patent Examiner, Art Unit 4131

Geeta Kadambi
Examiner
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